REMARKS

1. Maintained Objections and Rejections

The Examiner indicated that claims 1, 5, 7-9, 12-14, and 17-19 were still rejected under 35 USC §102b as being anticipated by Coutsoudis et al. or Barrett et al., or Japanese patent 60/197,669.

The Applicants reassert their previous arguments about the effectiveness of the technical data taught by these references. The phrase "experiencing excess free radical generation" is well understood by persons of ordinary skill in the art, and is identifiable with a particular patient population. Attached to this response is Appendix A which lists (a) references quoted in the specification which teach oxidant states secondary to excess free radical or inadequate antioxidants in disease states associated with preterm delivery, and (b) additional references (not cited in the original specification) which show that preterm delivery and associated disease states are also associated with oxidant stress. This supports the Applicants position that the specifications teaches how to identify such a patient.

Further, these claims, and all claims in the Application, have been amended to delete the phrase "improved method" or "improved therapy." Therefore, the amended claim overcome the Examiner's objection to this phraseology.

2. New Rejections

(a) Claim Objections:

(1) Claims 2, 4, 10 and 11 were rejected for certain informalities relating to spelling and lack of clarity (for example "NAC"). These have been corrected in the amended claims.

(2) Claims 2, 4 and 11 were further objected to for dependency on rejected claims. New claim 23 appropriately correct this by rewriting the new claim to in independent form.

(3) Claims 1-18 and 20-21 were objected to because the claims recited an improved method but did not follow the proper form. As previously addressed in paragraph 1 above, this objectionable phraseology has been deleted.

(b) 35 USC §112 Rejection: Claims 1 and 6 were rejected under Section 112 as being indefinite because of the phrase "improve outcome of premature labor." This phraseology has also been corrected. One of ordinary skill in the art would readily understand this phrase as it appears in the specifications to mean "delaying delivery to closer to the due date for delivery." Therefore, the amendment of the claims is not the introduction of new matter into the application.

(c) 35 USC §102 Rejections: Claims 6, 10, 20 and 21 were rejected under 35 USC §102(a) as being anticipated by Yallampalli et al. The Applicants would point out that a careful reading of the Yallampalli reference only discloses the term "salicylate" once in the entire reference and this is to aspirin. The aspirin is defined as an anti-inflammatory agent which inhibits prostaglandin synthesis. There is no linkage or reference whatsoever with its potential as an antioxidant or its ability to trap free radicals (i.e., a spin trapping agent). It appears that the Examiner assumes that all salicylates are spin traps. This is not true. There is teaching that aspirin does not act as an antioxidant or as a spin trap. See Appendix B.

Yallampalli refers to aspirin, acetyl salicylic acid, which is not a good trap. Some salicylates make good traps (such as phenols or phenoxides), because they have a free OH group to react with the free radical by loosing an electron and generating arroxyles (arryloxides). In aspirin (cited by Yallampalli) the OH group is acetylated and is thus blocked from reacting with the radical. Amended claims 6, 10, 20 and 21 now claim a spin trapping free radical scavenger.

3. Conclusion

The Applicants have amended the claims to overcome the prior art cited. They respectfully request that the Examiner reconsider these amended claims. Finally, the Applicants ask the Examiner to issue a Notice of Allowance.

Respectfully submitted,
JACKSON WALKER L.L.P.

Thomas E. Sisson, Reg. No. 29,348
112 E. Pecan Street, Suite 2100
San Antonio, Texas 78205
Phone: (210) 978-7700
Fax: (210) 978-7790
Attorneys for Applicant

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References quoted in the initial filing for oxidant states secondary to excess free radicals or inadequate antioxidants in the following disease states associated with preterm delivery:

Preterm labor

Gryglewski RJ, Palmer RM, Moncada S Superoxide anion is involved in the breakdown of endothelium-derived vascular relaxing factor. Nature 1986; 320(6061): 454-6 (modifying bioavailability of nitric oxide)

Buhimschi et al., 1996

Endotoxemia

Peristeris P, Clark BD, Gatti S, Faggioni R, Mantovani A, Mengozzi M, Orencole SF, Sironi M, Ghezzi P. N-acetylcysteine and glutathione as inhibitors of tumor necrosis factor production. Cell Immunol 1992; 140: 390-9.

Zhang H, Spapen H, Nguyen DN, Benlabed M, Buurman WA, Vincent JL. Protective effects of N-acetyl-L-cysteine in endotoxemia. Am J Physiol 1994; 266: H1746-54.

Cytokine release (which is associated with preterm labor)

DeForge LE, Fantone JC, Kenney JS, Remick DG. Oxygen radical scavengers selectively inhibit interleukin 8 production in human whole blood. J Clin Invest 1992; 90: 2123-9.

Cervical ripening (MMP activation)

Junqueira LC, Zugaib M, Montes GS, Toledo OM, Krisztan RM, Shigihara KM. Morphologic and histochemical evidence for the occurrence of collagenolysis and for the role of neutrophilic polymorphonuclear leukocytes during cervical dilation. Am J Obstet Gynecol 1980; 138: 273-81.

Birkedal-Hansen H, Moore WG, Bodden MK, Windsor LJ, Birkedal-Hansen B, DeCarlo A, Engler JA. Matrix metalloproteinases: a review. Crit Rev Oral Biol Med 1993; 4: 197-250.

Fortunato SJ, Menon R, Lombardi SJ. Collagenolytic enzymes (gelatinases) and their inhibitors in human amniochorionic membrane. Am J Obstet Gynecol 1997; 177: 731-41.

Parry S, Strauss JF 3rd. Premature rupture of the fetal membranes. N Engl J Med 1998; 338: 663-70.

Tyagi SC, Kumar S, Borders S. Reduction-oxidation (redox) state regulation of extracellular matrix metalloproteinases and tissue inhibitors in cardiac normal and transformed fibroblast cells. J Cell Biochem 1996; 61: 139-51.

Rajagopalan S, Meng XP, Ramasamy S, Harrison DG, Galis ZS. Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases in vitro. Implications for atherosclerotic plaque stability. J Clin Invest 1996; 98:2572-9. (effect of NO not the same as NAC)

Conditions at high risk for preterm labor

Cocaine use

Little BB, Snell LM, Klein VR, Gilstrap LC. Cocaine abuse during pregnancy: maternal and fetal implications. Obstet Gynecol 1989; 73:157-60

Feldman JG, Minkoff HL, McCalla S, Salwen M. A cohort study of the impact of perinatal drug use on prematurity in an inner-city population. Am J Public Health 1992; 82: 726-8.

Chasnoff IF, Burns WJ, Schnoll SH, Burns KA. Cocaine use in pregnancy. N Engl J Med 1985; 313: 666-9.

Zimmerman EF, Potturi RB, Resnick E, Fisher JE. Role of oxygen free radicals in cocaine-induced vascular disruption in mice. Teratology 1994; 49: 192-201

Alcoholism

Henderson GI, Chen JJ, Schenker S. Ethanol, oxidative stress, reactive aldehydes, and the fetus Review. Front Biosci 1999; 4:D541-50.

Kourie JI. Interaction of reactive oxygen species with ion transport mechanisms. Am J Physiol 1998; 275: C1-24.

Navasumrit P, Ward TH, Dodd NJ, O'Connor PJ. Ethanol-induced free radicals and hepatic DNA strand breaks are prevented in vivo by antioxidants: effects of acute and chronic ethanol exposure. Carcinogenesis 2000; 21: 93-9.

Kono H, Rusyn I, Yin M, Gabele E, Yamashina S, Dikalova A, Kadiiska MB, Connor HD, Mason RP, Segal BH, Bradford BU, Holland SM, Thurman RG. NADPH oxidase-derived free radicals are key oxidants in alcohol-induced liver disease. J Clin Invest 2000; 106: 867-72.

Tobacco use

Shah NR, Bracken MB. A systematic review and meta-analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. Am J Obstet Gynecol 2000;182: 465-72.

Kolas T, Nakling J, Salvesen KA. Smoking during pregnancy increases the risk of preterm births among parous women. Acta Obstet Gynecol Scand 2000; 79: 644-8.

Pourcelot S, Faure H, Firoozi F, Ducros V, Tripier M, Hee J, Cadet J, Favier A, Urinary 8-oxo-7,8-dihydro02'-deoxyguanosine and 5-(hydroxymethyl) uracil in smokers. Free Rad Res 1999; 30: 173-80

Laskowska-Klita T, Szymborski J, Chelchowska M, Czerwinska B, Chazan B. Compensatory antioxidant activity in blood of women whose pregnancy is complicated by cigarette smoking. Med Wieku Rozwoj 1999; 3: 485-94

Cerebral Palsy

Yoon BH, Jun JK, Romero R, Park KH, Gomez R, Choi JH, Kim IO 1997a. Amniotic fluid inflammatory cytokines (interleukin-6, interleukin-1beta, and tumor necrosis factor-alpha), neonatal brain white matter lesions, and cerebral palsy Am J Obstet Gynecol 177:19-26.

Additional references relevant but not in the original filing showing preterm delivery and associated disease states are also associated with oxidant stress:

Preterm delivery:

Buhimschi IA, Buhimschi CS, Pupkin M, Weiner CP. Beneficial impact of term labor: nonenzymatic antioxidant reserve in the human fetus. Am J Obstet Gynecol. 2003;189:181-8.

Buhimschi IA, Kramer WB, Buhimschi CS, Thompson LP, Weiner CP. Reduction-oxidation (redox) state regulation of matrix metalloproteinase activity in human fetal membranes. Am J Obstet Gynecol. 2000;182:458-64.

Weiss A, Goldman S, Ben Shlomo I, Eyali V, Leibovitz S, Shalev E. Mechanisms of matrix metalloproteinase-9 and matrix metalloproteinase-2 inhibition by N-acetylcysteine in the human term decidua and fetal membranes. Am J Obstet Gynecol. 2003;189:1758-63.

Lappas M, Permezel M, Rice GE. N-Acetyl-cysteine inhibits phospholipid metabolism, proinflammatory cytokine release, protease activity, and nuclear factor-kappaB deoxyribonucleic acid-binding activity in human fetal membranes in vitro. J Clin Endocrinol Metab. 2003;88:1723-9.

Buss IH, Darlow BA, Winterbourn CC. Elevated protein carbonyls and lipid peroxidation products correlating with myeloperoxidase in tracheal aspirates from premature infants. Pediatr Res. 2000;47:640-5.

Cambonie G, Hirbec H, Michaud M, Kamenka JM, Barbanel G. Prenatal infection obliterates glutamate-related protection against free hydroxyl radicals in neonatal rat brain. J Neurosci Res. 2004;75:125-32.

Lappas M, Permezel M, Rice GE. N-Acetyl-cysteine inhibits phospholipid metabolism, proinflammatory cytokine release, protease activity, and nuclear factor-kappaB deoxyribonucleic acid-binding activity in human fetal membranes in vitro. J Clin Endocrinol Metab. 2003;88:1723-9.

Gervasi MT, Chaiworapongsa T, Naccasha N, Blackwell S, Yoon BH, Maymon E, Romero R. Phenotypic and metabolic characteristics of maternal monocytes and granulocytes in preterm labor with intact membranes. Am J Obstet Gynecol. 2001;185:1124-9.

Matsubasa T, Uchino T, Karashima S, Kondo Y, Maruyama K, Tanimura M, Endo F. Oxidative stress in very low birth weight infants as measured by urinary 8-OHdG. Free Radic Res. 2002;36):189-93.

Bolisetty S, Naidoo D, Lui K, Koh TH, Watson D, Whitehall J. Antenatal supplementation of antioxidant vitamins to reduce the oxidative stress at delivery--a pilot study. Early Hum Dev. 2002;67:47-53.

Huel G, Campagna D, Girard F, Moreau T, Blot P. Does selenium reduce the risk of threatened preterm delivery associated with placental cytochrome P450-1A1 activity? Environ Res. 2000;84:228-33.

Lipton JW, Gyawali S, Borys ED, Koprich JB, Ptaszny M, McGuire SO. Prenatal cocaine administration increases glutathione and alpha-tocopherol oxidation in fetal rat brain. Brain Res Dev Brain Res. 2003 30;147:77-84.

Agents Actions. 1987 Jun;21(1-2):191-4. Related Articles, Links

The antiinflammatory moiety of sulfasalazine, 5-aminosalicylic acid, is a radical scavenger.

Ahnfelt-Ronne I, Nielsen OH.

Using a novel spectrophotometric assay to detect free radical scavengers, the effects of sulfasalazine, a compound frequently administered in the treatment of chronic inflammatory bowel disease, and its main metabolites, 5-aminosalicylic acid (5-ASA), sulfapyridine, and N-acetyl-5-ASA, were compared with biological antioxidants (nordihydroguaiaretic acid (NDGA), alpha-tocopherol, and ascorbic acid) and antiinflammatory salicylates (acetylsalicylic acid and sodium salicylate). The results show that 5-ASA, but neither sulfasalazine and its other metabolites, **nor the salicylates**, shares with the biological antioxidants the property of being a potent scavenger of free radicals. Since 5-ASA is formed in millimolar concentrations in the colon of sulfasalazine-treated patients this mode of action may explain the beneficial effect of sulfasalazine in inflammatory bowel disease. Locally formed 5-ASA may break the free radical chain reaction initiated and maintained by activated phagocytes, thus arresting the perpetuating tissue destruction. This mechanism may indicate a general potential for radical scavengers in chronic inflammation.

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